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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WOITACH, JOSEPH T	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 09/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

File

Office Action Summary	Application No.	Applicant(s)	
	09/534,487	REID ET AL.	
	Examiner	Art Unit	
	Joseph T. Woitach	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21,23,25,27,29-36 and 39-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21,23,25,27,29-36 and 39-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9, 20* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on June 27, 2003, paper number 24, has been entered.

DETAILED ACTION

This application is a continuation of 09/115,920, which has been allowed, which is a continuation of 08/751,546, now Patent No. 5,789,246, which is a divisional of application 8/165,696, now patent 5,576,207, which is a continuation 7/741,128, now abandoned.

As indicated in applicants' request for continued examination the after final amendment filed December 5, 2002, paper number 20, has been entered. Claim 22 has been canceled. Claims 21, 23, 25, 27, 29, 39, 40 have been amended. Claims 41-43 have been added. Claims 21, 23, 25, 27, 29-36, 39-43 are pending and currently under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21, 23, 25, 27, 29-36, 39-43 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is noted that claims 21, 23, 25, 27, 29-36, 39-43 have been amended to encompass a method of treatment of liver dysfunction in a subject comprising administering a genetically engineered hepatocyte precursor to the subject. More specifically, the claims now encompass only a method of *ex vivo* gene therapy wherein the hepatocyte precursor cells are first removed, genetically modified with a polynucleotide then returned to a subject for the treatment of any liver dysfunction with said genetically modified hepatocyte precursor cells. The dependent claims recite that administration of said cells may be through injecting, transplanting, or grafting said cell into the subject, in particular the liver or the spleen (claim 25). Further, dependent claims recite that the gene of interest can be inserted into the genome of the cell or maintained extrachromasomally (claims 31 and 32) and recited a list of diseases for which said methodology could be used (claim 34). Finally, it is noted that the claims encompass administering 'autologous' (claim 28) and 'histocompatible normal' (claim 41) hepatocyte precursor cells.

Initially, Examiner agrees with Applicants arguments that amendments to the claims to be drawn to administering autologous and histocompatible cells obviates the basis of the rejection which focuses on the rejection of engrafted cells in a subject due to the immune reaction generated to cells comprising foreign antigens. Further, the amendments to the claims to encompass only *ex vivo* gene therapy methodology obviates the basis of the rejection which focuses on the failure of the instant disclosure to remedy the art recognized limitations for *in vivo* gene therapy protocols.

Two main points of enablement are at issue; first, the ability of the disclosed composition of precursor cells to serve as hepatocyte precursor cells for treatment when placed into a subject, and second the lack of necessary guidance and skill in the art to provide treatment of a specific liver dysfunction by genetically engineering a hepatocyte precursor cell.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (MPEP 2164.01(a)). The

specification is not enabling for the claimed invention because the specification does not provide sufficient guidance, evidence or exemplification so that an artisan of skill would have been able to make and use the invention as claimed invention without undue experimentation.

The specification teaches the isolation of a composition of cells which comprises hepatocyte precursor cells from the liver (entire specification, summarized on page 2; lines 1-5), and that culturing the precursor cells with liver stromal cells and an extracellular matrix one can effectively increase the number of said precursor cells (summarized on page 7; lines 13-18). However, the specification only provides conditions and methods for isolating the precursor cells in the context of a composition of cells (see for example US Paten 6,146,889) and does not provide any guidance to isolate a population of hepatocyte precursor cells as a starting material as required by the instantly claimed methods or as present in the drug delivery system of claim 40. The specification provides evidence that hepatocyte precursor cells exist in a composition of cells isolated from total liver, however the specification fails to provide the necessary guidance or details on how one would isolate the materials, i.e. hepatocyte precursor cells, to practice the instantly claimed method or make the drug delivery system. More importantly, the specification does not provide any substantive teaching nor examples demonstrating that hepatocyte precursor cells isolated in this manner will maintain a precursor like state or will differentiate into mature hepatocytes *in vitro* or *in vivo* if engrafted back into a subject. The specification presents only a prophetic description for the potential use of the hepatocyte precursor cells in obtaining a genetically engineered hepatocyte precursor but does not demonstrate that one can isolate, culture

or place these cells back into an *in vivo* context in a subject by any means as required by the instant claims.

In addition, it is noted that the term "hepatocyte precursors" recited in the claims is not specifically defined in the specification, however is indicated to be used to describe a cell population that "has been culture under conditions which result in expansion of the immature cells" (page 1, lines 16-17). This term as broadly described and supported by the instant specification encompasses immature cells from any source obtained by any means. This interpretation of the breadth of the claim is more specifically supported by the specification stating that the precursor cells can be obtained sources other than the liver, "sources, such as, but not limited to, the pancreas, gut, lung, and bone marrow" (page 1, lines 22-24). The specification provides no specific epitopes for the contemplated precursor cells, potentially supporting only the absence of specific genes which are expressed in more differentiated cells. As noted in Applicants' arguments, Examiner acknowledges 'that the capability of a hepatocyte precursor cells to differentiate into a hepatocyte "is a necessary and defining characteristic of a hepatocyte precursor cell" (Applicants' after final amendment top of page 11; Examiners action paper number 7, page 13), however the specific basis of the rejection is that the specification fails to provide the necessary guidance or details of the identifying features of these cells which are indicative or predict this characteristic. The specification provides general guidance for mincing and dissociating cells of a tissue, and reduces to practice the culturing of a composition of cells isolated from liver. At the time of filing and today the artisan believed that the liver contained

stem cells, therefore it would not be contested that the facile methodology reduced to practice resulted in a composition of cells which comprised hepatocyte precursor cells, however while stem cells may exist in other tissues there is no evidence of record that hepatocyte precursor cell exists in other tissues. Further, while other culturing conditions are generally contemplated, the specification fails to provide the means to these specific conditions. Moreover, without any specific or defining feature of a hepatic precursor cell maintained in the disclosed composition of cultured cells, the skilled artisan would not even be able to optimize conditions if such a precursor cell existed in tissues other than the liver. Examiner acknowledges the subject matter that has been set forth in US patents to which the instant application claims priority, however the subject matter determined to be enabled and patentable is not equal in scope with that instantly claimed. Importantly in this case, the instant claims do not use or require the composition of cells claimed in US patent 5,789,246. Further, it is noted that patentability of a product only requires one enabled use and does not by itself enable all potential uses of said product, and therefore would not provide a presumptive rebuttal of a *prima facie* case of lack of enablement for any method using said product. In this case the claims to the allowed product are not the same as the product used in the instantly claimed methods, nor does the existence of such a cell in a composition provide for any prophetic use of said cell.

Finally, Applicants have provided several post filing references for support of use of stem cells in therapeutic methods, in particular for the delivery of a transgene. The ability to make a genetically altered cell by transforming a cell with a gene of interest in culture is not at issue.

Examiner acknowledges that specific methodology for models of *ex vivo* gene therapy are currently being developed in the art. With respect to the references provided by Applicants, the only reference relevant to the instantly claimed method is that of Dabeva *et al.* because the remaining references deal with hematopoietic stem cells not hepatocyte precursor cells. Hematopoietic stem cells are present in the circulation or bone marrow and can only be used in particular therapies associated with lineages of these cell types. None of the specific methodology or genes of interest for this technology would be applicable to the instantly claimed methods. With respect to the teachings of Debeva *et al.* initially it is noted that the FLEC used by Debeva *et al.* are not the same as used in the instantly claimed methods, nor are they obtained by the methods disclosed in the instant specification therefore does not by itself provide evidence that the cells disclosed in the instant specification and used in the instantly claimed method would differentiate into hepatocytes when placed into the liver of a subject. Even if one to concede that the hepatocyte precursor cells present in the composition of cells enabled by the instant application would differentiate *in vivo*, Debeva *et al.* teach that the method needed to successfully engraft cells into the liver require partial hepatectomy which is not taught in the instant specification. The specification recites the potential usefulness of genetically engineered hepatocyte precursor cells for treatment of liver dysfunction, and provides a curt description of methodology for inserting a gene of interest and administering said cell for treatment, wherein treatment is affected by expression of a missing or mutated endogenous gene, expression of antisense polynucleotides to suppress expression of an undesired gene (pages 12-14; starting at

line 4). With respect to instant application, there is no specific guidance nor examples on how one would treat any liver dysfunction. For example, the specification provides a general description of how one could treat hypercholesteremia by expressing the LDL gene in said cells, however there is no specific guidance on the type of promoter to use, the level of LDL expression one would need to treat a subject or if these cells would proliferate in a subject, how many cells to transplant. Another example describes the treatment of hepatitis infection by expression of anti-sense polynucleotides, however there is no guidance to what oligonucleotides would generate any treatment, what levels of expression one need to inhibit any function of any aspect of viral pathology, or how expression of a polynucleotide in a transplanted cell would affect any form of treatment in other surrounding cells. There is no guidance in the specification nor the art of record on how one would target and insert a gene of interest into said cells to create a genetically modified cell. The present specification has not provided any guidance to serve as a nexus between the art recognized obstacles of gene therapy protocols and treatment of any liver dysfunction.

Besides the general expectation that it will require years of further research to develop effective gene therapy (Anderson, page 30), it would require extensive research to understand the fundamental biology of the system. Applicants have described a method to isolate a composition of cells comprising hepatocyte precursor cells from the liver, however essentially all of the work required to genetically engineer the cells with the appropriate gene for a particular liver

dysfunction, use of the cells for treatment *in vivo*, and the proper route of administration to affect treatment has been left for others.

In view of the of the lack of guidance, working examples, breadth of the claims, skill in the art and state of the art at the time of the claimed invention, it would require undue experimentation by one of skill to practice the invention as claimed.

New Matter

Claims 21, 23, 25, 27, 29-36, 39- 40 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is withdrawn.

As indicated in the advisory action mailed December 17, 2002, paper number 21, Applicants' arguments and the literal support for 'autologous grafting' (specification, page 10, line 10) is sufficient to overcome the new matter rejection.

Claims 41 and 42 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The added material which is not supported by the original disclosure is drawn to using 'a histocompatible normal hepatocyte precursor cell'. Applicants do not point to the literal support for the term 'histocompatible' and upon review of the instant specification Examiner can not identify specific support for this term. It is noted that Applicants argue that support "for the use of the term "histocompatible" is found inherently in the specification and art acknowledged by Examiner" (Applicants' after final amendment, page 5, middle of the page). Applicants' arguments have been fully considered but not found persuasive.

While Examiner would agree that the skilled artisan in the art of transplantation would recognize many of the limitations for transplantation the teachings of the instant specification for the use of hepatocyte precursor cells actually teaches away for the concern of this potential problem in particular the teaching that 'administration of such immature cells may also be less likely to stimulate immune rejection'. Further, the specification teaches that cells from one source and that the 'expanded hepatocyte precursor obtained from one liver may thus be administered therapeutically to a plurality of patients'. Neither specific teaching in the specification supports the need or intent of using a 'histocompatible' precusor liver cell. As noted above, the term 'autologous' finds literal support in the present specification, however this term would not encompass the breadth of the term encompassed by 'histocompatible'. Further, while it provides the literal support for the use of the term in method claims, it does not teach that this is a preferred embodiment or requirement to practice the instantly claimed methods. To the contrary, the teaching that the precursor cells disclosed in the present specification are 'less

likely to stimulate immune rejection than the injection of mature hepatocytes' (page 15, lines 9-10) implicitly teaches that concern of immune reactions to administered precursor cells would avoid the problems recognized in the art that are associated with administering mature cells (hepatocytes) to a subject.

Applicant is required to cancel the new matter in the reply to this Office action.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21, 23, 25, 27, 29-36, 39-40 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn.

The amendments to the claims has obviated the basis of each of the specific rejections.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (703)305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (703) 308-2141.

Joseph T. Woitach

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